

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup>:</b> <b>A61K 49/00</b>	<b>A2</b>	<b>(11) International Publication Number:</b> <b>WO 97/45145</b> <b>(43) International Publication Date:</b> 4 December 1997 (04.12.97)
<b>(21) International Application Number:</b> PCT/GB97/01461 <b>(22) International Filing Date:</b> 29 May 1997 (29.05.97) <b>(30) Priority Data:</b> 9610971.5 29 May 1996 (29.05.96) GB <b>(71) Applicant (for all designated States except US):</b> SCOTIA HOLDINGS PLC [GB/GB]; Weyvem House, Weyvem Park, Portsmouth Road, Peasmarsh, Guilford, Surrey GU3 1NA (GB). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> GLEN, Alexander, Iain, Munro [GB/GB]; Dalnavert Farm House, Feshiebridge, Kincaig PH21 1NQ (GB). WARD, Pauline, Elizabeth [GB/GB]; 43 Muirfield Road, Inverness IV2 4AY (GB). HORROBIN, David, Frederick [GB/GB]; Scotia Pharmaceuticals Limited, Scotia House, Castle Business Park, Stirling FK9 4TZ (GB). <b>(74) Agent:</b> PHILLIPS & LEIGH; 7 Staple Inn, Holborn, London WC1V 7QF (GB).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>
<b>(54) Title:</b> A DIAGNOSTIC TEST FOR SCHIZOPHRENIA, USING NIACIN		
<b>(57) Abstract</b>		
<p>Niacin in the form of a topical preparation, both as such and when incorporated in devices for application to the skin; the devices themselves; diagnosis or monitoring of schizophrenia using the preparations or devices; and manufacture of medicaments for such monitoring and diagnosis.</p> <div data-bbox="818 1205 980 1299" data-label="Chemical-Block"><p>The chemical structure of Niacin (Vitamin B3) is shown, consisting of a pyridine ring with a carboxylic acid group (-COOH) attached to the 3-position.</p></div>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

## A DIAGNOSTIC TEST FOR SCHIZOPHRENIA, USING NIACIN

Field of Invention

The invention relates to a diagnostic test for use in schizophrenia.

5

Background

Schizophrenia is a common psychiatric disease which in most populations affects about 1% of the population. There are many different clinical presentations of the disease which can be broadly divided into two main groups, the "positive" features and the  
10 "negative" or "deficit" features. The positive features include auditory hallucinations, bizarre behaviour, thought disorder and sometimes paranoia. The negative features include social and emotional withdrawal and an absence of emotional responses to what is happening in the individual's environment. Some of these features are shared by other psychiatric disorders and, especially in the early years of the disease, it may be difficult to  
15 distinguish schizophrenia from depression, manic-depression, drug-induced psychoses and psychoses related to alcoholism. Only the long term course allows a diagnosis of schizophrenia to be made with reasonable certainty. This diagnostic uncertainty in the early stages of the disease has important practical consequences because therapies for the different disorders differ and the uncertainty may delay, sometimes for many years, the  
20 introduction of optimum therapy. A biochemically based test which would improve early diagnosis would therefore be of great value.

There is evidence that in schizophrenia there is a biochemical abnormality in the metabolism of the fatty acids of membrane phospholipids to prostaglandins (Horrobin DF,  
25 Lancet 1:936-7, 1977; Horrobin DF, Glen AIM, Vaddadi KS, Schizophrenia Research, 1994). In particular, in schizophrenics with the deficit syndrome there is a substantial reduction in the concentrations of arachidonic acid (AA) and docosahexaenoic acid (DHA) in red cell membranes (European Patent Application 0599576). There are also peculiarities in the cPLA2 (phospholipase A2) gene structure (PCT patent application  
30 No.97/04127).

Niacin (nicotinic acid) is a vitamin which, when given in a large oral dose, causes marked flushing of the skin over the head, upper body and arms. This flushing is due to vasodilation caused by the release of prostaglandin D<sub>2</sub> from AA. In 1980, Horrobin noted that whereas most normal individuals flush markedly in response to 100-300mg niacin given orally, a substantial proportion of schizophrenics fail to flush. Many but not all of the non-flushing individuals were patients with the deficit syndrome. Horrobin therefore suggest that a flushing response to oral niacin might be used as to assist diagnosis of schizophrenia (Horrobin DF, Journal of Orthomolecular Psychiatry, 9: 33-34, 1980). The idea was that individuals who showed a pattern of behaviour possibly indicative of schizophrenia and who failed to flush in response to niacin would almost certainly have schizophrenia. Individuals who did flush might or might not have the disease. However, in non-flushers appropriate therapy could be introduced without delay. Horrobin also noted that some patients whose schizophrenia improved on being treated with essential fatty acids shifted from a non-flushing to a flushing response and he suggested that flushing could be used as an indicator of improvement in response to treatment. Other investigators have confirmed that a substantial proportion of schizophrenics fail to respond to a fixed oral dose of niacin by flushing (Rybakowski J et al, Biological Psychiatry, 29: 834-61, 1990, Hudson J et al, Biological Psychiatry, 41: 507-13, 1997). However, there are several drawbacks to the oral test. The flushing reaction is usually accompanied by pricking and tingling sensations which can be quite distressing and there can be a fall in blood pressure. In particular, in paranoid patients the responses may arouse suspicion and hostility. Further, the oral treatment involves a single, all or nothing response which is difficult if not impossible to quantify.

## The Invention

We have now surprisingly found that the oral test can be replaced by a simple test involving the application of different concentrations of niacin in any effective form, or even a single chosen concentration, to the skin. This is easy to apply, and causes no distress. The test is quickly read, for example in 3 to 6 minutes with a negative reaction desirably checked after 15 minutes in contrast to the 30-60 minutes which may be required for the

oral test. Further, it is not affected by whether or not the individual being tested has a full stomach, and it can be made quantitative.

5 The invention in its various aspects is set out fully in the claims, to which reference should be made, but may be summarised as niacin in the form of topical preparations, both as such and when incorporated in devices for application to the skin; the devices themselves; diagnosis or monitoring of schizophrenia using the preparations or devices; and manufacture of medicaments for such monitoring and diagnosis.

10 The test involves the topical application of niacin solutions, preferably in a carrier such as gauze, cotton, wax or appropriate fibre or absorbent material, to the skin of any part of the body, but conveniently the forearm or upper arm. A range of solutions may be used from 0.00001M to 1 molar. A single concentration may be chosen and used but desirably use is made of a range of steps varying from two to twenty. We have found it convenient  
15 to use a range of four solutions of 0.1, 0.01, 0.001 and 0.0001M, e.g. 0.05 ml of each, but other concentrations within the range and other numbers of steps can be used as found appropriate, both in diagnosis and in monitoring as discussed above. It is particularly convenient to incorporate the niacin-impregnated patches into a plastic or other strip, wherein the individual patches range for example from 1 to 20mm in diameter, and  
20 wherein the patches are in individual wells or depressions which may be anything from 0.5mm to 20mm apart, preferably 2-10mm apart. The wells or depressions may be sealed by another plastic or other strip which isolates them from the atmosphere and which can be removed immediately prior to testing. The strip with the open wells can then be applied to the skin surface with light pressure and removed after an appropriate time which may be  
25 e.g. 0.5 minutes up to 10 or 15 minutes but preferably 3 to 6 minutes.

In normal individuals, after a short time, an adequate topical concentration of niacin produces both redness (flushing) of the skin and skin swelling (oedema). Both of these effects are due to vasodilatation of the small blood vessels of the skin. The redness may be  
30 scored in relation to the adjacent unaffected skin on an appropriate scale which can be either "present" or "absent", or can be semi-quantitative, such as mild, moderate or marked, or can be made fully quantitative by use of a spectrophotometer or other appropriate

instrument e.g. a blood flow meter. The oedema can likewise be scored as present or absent or can be scored semi-quantitatively or quantitatively.

We have applied this test to 38 patients with schizophrenia and 22 controls, using  
 5 niacin concentrations of 0.1, 0.01, 0.001 and 0.0001M, 0.05 ml of each, and time intervals of 0, 5, 10, 15, 20 and 25 minutes after application of the niacin containing patches. We have also used a scoring system in which the degree of redness under each patch was scored as 0 = no change, 1 = mild redness, 2 = moderate redness and 3 = marked redness. When the test is used commercially, sample colour charts may show how the test can be  
 10 used with individuals of varying skin colour. With particularly dark-skinned individuals, oedema or a measurement of skin surface temperature or heat loss may be required to give the best results.

Table 1 shows the scores obtained in the two groups at 5 minutes after application  
 15 of the test, a time showing good discrimination between the groups:

Table 1 Percentages of normal controls (n=22) and of schizophrenics (n=38) responding at 5 minutes to the application of topical niacin with absent [0], mild [1], moderate [2] or marked [3] reddening of the skin, C=controls and S=schizophrenics.

20

#### Niacin Concentrations

	0.1M		0.01M		0.001M		0.000.M	
	C	S	C	S	C	S	C	S
25								
Response								
Absent [0]	4.5	13.5	9.1	41.2	31.8	67.6	35.3	88.2
Mild [1]	9.1	37.8	13.6	41.2	9.1	29.4	29.4	8.8
30 Moderate [2]	27.3	43.2	45.5	17.6	40.9	2.9	17.6	2.9
Marked [3]	59.1	5.4	31.8	0	18.2	0	17.6	0

As may be seen, the three lower concentrations do not give a marked reaction in any  
5 of the schizophrenics. Even a moderate reaction, at the two lower concentrations, is shown  
by very few of the schizophrenics, the great majority showing a mild reaction or none. In  
contrast, only 4.5% of the normal individuals failed to give a response even to the highest  
concentration. Given the difficulty of making a secure diagnosis of schizophrenia, the  
indication given by the new test is thus highly valuable, for use in conjunction with other  
10 criteria. A valuable feature is that the test, as with oral niacin (Rybakowski J et al,  
Biological Psychiatry, loc. cit.) may be expected to give a response in depressives the same  
as for normal individuals.

Suitably the niacin is in aqueous solution in the form of a  $C_1$  to  $C_{10}$  alkyl ester such  
15 as the methyl or hexyl ester but any effective form that is to say a form passing the skin and  
eliciting the flushing reaction in normal individuals, may be used. Nicotinamide  
(niacinamide), which does not elicit the reaction, is not suitable.

In the drawings:-

20

Figure 1 is a simple device for application by hand;

Figure 2 is a cuff-style device with a hook and loop ("Velcro" trade mark)  
fastening; and

25

Figure 3 is a section of part of Figure 1, taken axially of the strip at the right hand  
end as seen.

In the drawings, which are merely of examples of ways of using the invention, a  
30 moulded flexible plastics strip 1 has wells 2, each holding a gauze pad 3 impregnated with  
methyl nicotinate solution at the successive concentrations of Table 1. The pads are 16 mm  
diameter and approximately 1.5 mm thick. A backing strip 4 is secured by pressure

sensitive adhesive, to be peeled off when the device is to be used. After peeling, the device is applied to the body, conveniently to the forearm, with the pads in contact with the skin. The device may be held under finger pressure (Figure 1, one finger to a pad) or by the fastening (Figure 2), the two parts of which are indicated at 6 and 7, and the extent of the backing strip at 5. After for example 5 minutes, the device is removed and the skin reaction assessed as already described..

CLAIMS

5

1. Niacin as a topical preparation giving absorption of the niacin in any effective form through the skin, with production of a differential effect, as between schizophrenics and non- schizophrenics, in redness and swelling of the skin.

10

2. A preparation as in claim 1, wherein the niacin is in the form of a C<sub>1</sub> - 10 alkyl ester particularly C<sub>1</sub> - C<sub>6</sub> and most particularly methyl.

15

3 A preparation as claim 1 or 2, presented as two or more sub-preparations with the niacin in differing concentrations.

20

4. A preparation as in claim 1, 2 or 3, held in a carrier in a sealed device which, after removal of the seal, can be applied to the skin to bring the preparation into contact with the skin.

25

5. A method of manufacture of a medicament for the diagnosis or monitoring of schizophrenia by observation of a differential effect in redness and swelling of the skin as between schizophrenics and non-schizophrenics, wherein niacin in any effective form is incorporated in a topical preparation giving absorption of the niacin through the skin.

30

6. Diagnosis or monitoring of schizophrenia by observation of a differential effect in redness and swelling of the skin as between schizophrenics and non-schizophrenics, following application of niacin in any effective form in a topical preparation giving absorption of the niacin through the skin.

7. A method as in claim 5, or diagnosis or monitoring as in claim 6, wherein the preparation is as set out in claim 3 or 4.

8. Method, or diagnosis or monitoring, as in claims 5 to 7, wherein the redness is  
5 observed visually in terms of colour or by temperature measurement or heat loss, and is scored against a pre-prepared scale.

9. Preparation, method, or diagnosis or monitoring as claimed above, using concentrations(s) of niacin 0.0001 to 0.1 M.

10

10. Preparation method, or diagnosis or monitoring as claimed above, with observation of the effect after 0.5 to 10 minutes following application to the skin, more conveniently 3 to 6 minutes, with a negative response optionally checked after 15 minutes.

11. Preparation, method or diagnosis or monitoring as claimed above, using a  
15 preparation held as in claim 4, wherein the device is a flexible strip holding the preparation in a well, or a plurality of spaced wells with differing niacin concentrations, and the seal is a removable cover film the flexible strip being suited after removal of the film for application to the skin with the carrier in contact with the skin.

20

12. As such, the device set out in claim 4 or 11, optionally in association with a colour chart, for scoring skin flushing reaction, or other pre-prepared quantifying aid.

25

FIG.1

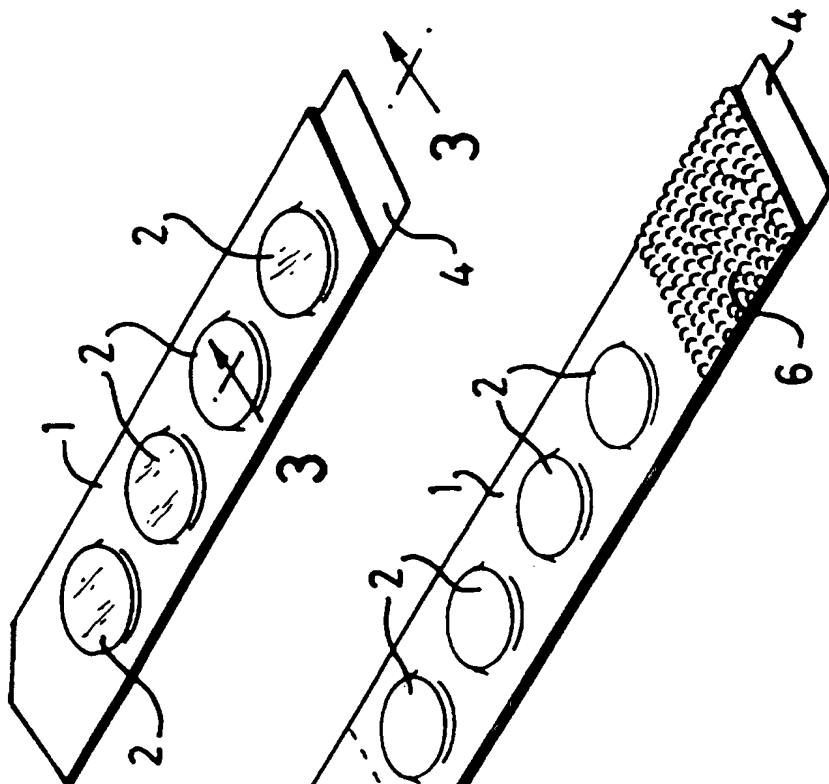


FIG.2

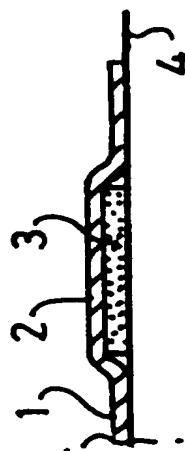
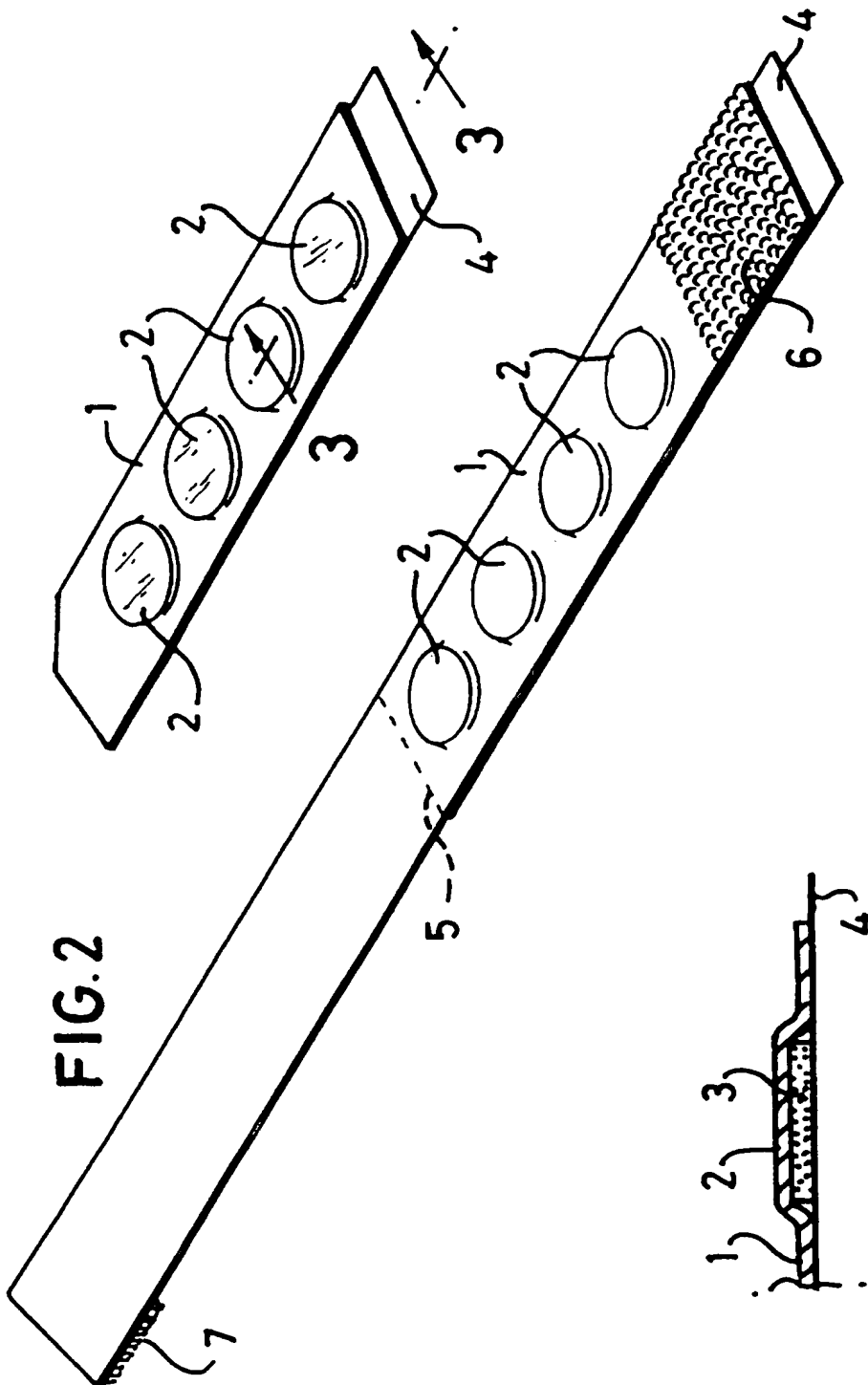


FIG.3